Narrative Review
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Researching the Phenomenon of Poor Ovarian Responders and Management Strategies in IVF: A Narrative Review

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Abstract
This narrative review aims to summarize all the latest studies published between 2015-2021 concerning the management protocols adopted for poor ovarian response (POR) cases. Patients defined as "poor responders" show minimal response to controlled ovarian hyperstimulation, although there is no standard definition for POR. Although infertility specialists are endeavoring to improve cycle outcomes in poor responders by adopting multiple management strategies, still the estimated risk of cycle cancellation is about 20%. All the studies performed during this study period were evaluated and their results were recorded. The latest published protocols to improve oocyte retrieval in poor responders include: anti-Müllerian hormone, clomiphene citrate, co-enzyme $Q_{10,}$ corifollitropin, dehydroepiandrosterone, double stimulation, Follicle Stimulation Hormone, Growth Hormone, Gonadotropin-releasing hormone agonists, letrozole, human chorionic gonadotropin, Luteinizing Hormone, progesterone and testosterone. **Conclusion.** Although many strategies have been suggested to manage POR, none has been proven superior to the others. Further large-scale randomized studies are needed to validate experimental techniques leading towards successful individualized treatment regimens.

Key Words: Poor Ovarian Response ▪ Assisted Reproduction Technology ▪ Controlled Ovarian Hyperstimulation ▪ Bologna Criteria ▪ POSEIDON (Patient-Oriented Strategies Encompassing Indivindualized Oocyte Number) Classification.

Introduction

Assisted reproduction technology (ART) has given hope to millions of couples suffering from infertility since the first In Vitro Fertilization (IVF) baby was born in 1978. Infertility experts strive to maximize reproduction success rates (1). However, IVF has lower success rates in women who respond poorly to Controlled Ovarian Hyperstimulation (COH), and they are described as "poor responders" (2). The proposed mechanism behind this condition seems to be a diminished ovarian reserve due to advanced maternal age, as well as a lower number of follicles sensitive to Follicle Stimulation Hormone (FSH) (2). Other causes have also been documented, from follicles insensitive to exogenous gonadotrophins, or suboptimal exposure attributed to obesity (2). Poor ovarian response has a high occurrence rate. According to the existing literature, poor responders have an incidence rate ranging from 9% to 24% (3). This considerably significant percentage could be attributed to the heterogeneity of the population of poor responders, since every IVF center adopts different criteria to categorize them (3). Data pooled from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology (ASRM/SART) Registry recorded a 14.1% cancellation rate of IVF

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cycles, with 50% representing women classified as poor responders (4).

Regarding ovarian aging, irreversible damage accumulates on the molecular level due to oxidative stress in the normal ovarian metabolism (5). Researchers consider the subject of therapy for poor ovarian response to be most pressing, as the rate of pregnancy decreases proportionally with the decreasing number of female gametes that can be isolated (3). Notably, advanced reproductive age, along with potential ovarian functional decline, may be associated with Reactive Oxygen Species (ROS) accumulated due to oxidative stress, one of the most important factors of cellular injury (5). In this context, the reduced potential of gametes developed in advanced female age has also been investigated (3).

The classification of a poor responder was first attempted by Garcia et al. in 1983 (6), who defined it as a person who, on a standard stimulation regimen (150 IU human menopausal gonadotrophin), had a peak estradiol concentration of <300 pg/mL and who had poor follicle production, leading to a smaller number of eggs retrieved and transferred. Currently, there is no consensus on the definition of the poor responding patient, or any effective treatment protocol for their management (7). Poor ovarian response is responsible for 20% of cancellations in assisted conception treatment cycles (3). However, existing evidence suggests that GnRH agonist protocols may reduce this rate significantly (8, 9).

This narrative review aims to provide an overview of the currently available management strategies for POR for IVF.

Definition and Aetiology of Infertility

Infertility is the failure of conception after 12 months of intercourse without contraceptive precautions (10). It affects 15% of couples worldwide (10). Primary infertility refers to the infertility of a couple who have never been able to conceive, whereas secondary infertility is the failure to conceive following a previous pregnancy (11). According to the WHO, more than 187 million married women suffered from primary or secondary infertility in the developing world in 2002 (11).

The most common causes of female infertility can be classified into categories based on the anatomy of the female genital tract, and are therefore categorized as: uterine, tubal, cervical or due to ovulation abnormalities. Uterine abnormalities include: leiomyomas, adenomyosis, intrauterine adhesions, endometrial polyps and Mullerian anomalies. Tubal abnormalities include: tubal occlusion, endometriosis and PID (Pelvic Inflammatory Disease). Cervical abnormalities include infertility due to cervical factors, such as cervical stenosis. Ovulatory abnormalities include: androgenic disorders, polycystic ovarian syndrome, premature ovarian failure and ovarian dysgenesis (12).

Definition of POR; the Bologna Criteria

In 1983, the definition of patients as "poor responders" was first described (6), as mentioned above. After this, various researchers adopted different criteria in order to provide a definition of POR. POR has been defined as the presence of at least two of the following criteria (13):

a) age at least 40 years old or other risk factors for POR.
b) previous POR episodes (3 or less oocytes collected with a standard stimulation protocol).
c) Antral Follicle Count (AFC) less than 5-7 follicles or anti-Müllerian hormone (AMH) less than 0.5-1.1 ng/mL or an Ovarian Reserve Test with abnormal results.

The above criteria were introduced by the European Society of Human Reproduction and Embryology (ESHRE) as the "Bologna Criteria" in 2011 during an attempt to standardize the diagnosis of POR. However, since then the validity of these criteria has been questioned. The diagnosis of poor ovarian response encompasses a wide range of sub-populations due to different associated mechanisms. In a systematic review by Polyzos et al. in 2011, at least 41 different definitions of POR were reported in 47 randomized trials (11). AFC and AMH levels were included, with flexible cut-off values, due to the lack of consistency between them regarding the population of poor

responders. Notably, the Bologna criteria have failed to address the issue of oocyte quality versus quantity (14).

The Shift from Bologna to Poseidon Criteria

In an attempt to overcome these issues, the novel POSEIDON (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) criteria were proposed for classification of "low prognosis" patients (15). The POSEIDON criteria include female age, ovarian reserve markers (AMH, AFC, or both), as well as the number of oocytes retrieved in previous cycles of conventional ovarian stimulation, in order to classify poor prognosis patients into four groups (Table 1). The documentation of at least two POR episodes is sufficient to define a patient as a poor responder (7). Ferraretti et al. in 2011 suggested that at least two episodes of POR after maximal stimulation are sufficient to define a patient as a poor responder, in the absence of advanced maternal age or abnormal ORT (7). The lack of a universally established definition highlights the complexity of proposing the ideal ovarian stimulation protocol, in relation to younger or advanced age poor responders (16). The majority of the current strategies proposed in the international literature for ovarian stimulation are discussed below and summarized in Table 2.

Table 1. POSEIDON Classification

Group 1	Patients younger than 35 years old, presenting with adequate values of AFC ≥5, AMH≥1.2 ng/ml, and poor ovarian response
1a	With less than 4 oocytes retrieved, after standard ovarian stimulation
1b	With 4-9 oocytes aspirated/retrieved, after standard ovarian stimulation
Group 2	Patients older than 35 years old, presenting with adequate values of AFC ≥5, AMH≥1.2 ng/ml, and poor ovarian response
2a	With less than 4 oocytes retrieved, after standard ovarian stimulation
2b	With 4-9 oocytes aspirated/retrieved, after standard ovarian stimulation
Group 3	Patients younger than 35 years old, presenting with poor values of AFC<5, AMH<1.2 ng/ml, and poor ovarian response
Group 4	Patients older than 35 years old, presenting with poor values of AFC<5, AMH<1.2 ng/ml, and poor ovarian response

Table 2. Selected Studies (2015-2020) and Pharmacological Treatments for Ovarian Stimulation in PORs

Authors	Year	Study design	Sample size	Study population	Treatment	Outcome
Magnusson *et al.* (17)	2017	RCT	308	PORs	Adding AMH to a conventional protocol with GnRH agonist and recombinant FSH	The addition of AMH did not alter the rate of targeted ovarian response, 5-12 oocytes, or decreased the rate of ovarian hyperstimulation syndrome (OHSS) or cancelled cycles due to POR
Xu Y. *et al.* (22)	2018	RCT	186	POSEIDON Group 3 PORs	Pretreatment with coenzyme Q10	Better ovarian response to stimulation and embryological parameters
Kolibianakis EM *et al.* (25)	2015	RCT	79	Previous POR to stimulation (≤4 COCs) after maximal stimulation	Substitution of 150 μg corifollitropin alfa with 450 IU follitropin beta during the first 7 days of ovarian stimulation	The number of COCs (cumulus oocyte complexes) retrieved was not statistically different between the corifollitropin alfa and the follitropin beta groups
Elprince *et al.* (31)	2020	RCT	50	PORs	DHEA supplementation (25 mg/8 h for two consecutive cycles before induction of ovulation)	DHEA treatment showed a statistically significant improvement compared to the control group

Authors	Year	Study design	Sample size	Study population	Treatment	Outcome
von Horn *et al.* (38)	2017	RCT	80	IVF patients	Follicular flushing with the modified flushing system.	No increase in the number of oocytes was reported, only an increase in the duration of the procedure.
Madani *et al.* (40)	2018	Prospective Clinical Trial	121	PORs	Double stimulation by Letrozole, Clomid, hMG and GnRH-agonist	No significant difference between the number of oocytes retrieved after the first stimulation (combination of clomiphene and LZ) and the second stimulation (LZ alone)
Lefebvre *et al.* (43)	2015	Prospective randomized controlled nonblinded study	356	PORs	450 vs 600 IU/d gonadotropin	Gonadotropin of 600 IU/d does not improve outcome of IVF cycles compared with 450 IU/d.
Lattes *et al.* (46)	2015	Prospective, self-controlled study	106	PORs	GH supplementation (0.5 IU/day)	Increase in pregnancy rates
Bassiouny *et al.* (47)	2016	RCT	145	PORs	GH supplementation to the microflare stimulation protocol	The numbers of oocytes collected, metaphase II oocytes, and fertilized oocytes increased
Dakhly *et al.* (48)	2016	Prospective RCT	287	PORs	GH as an adjuvant therapy added to either long or short agonist protocol, miniflare or antagonist protocols	Long/GH showed significantly higher levels in the number of fertilized oocytes, than the short/GH and antagonist/GH protocols
Maged *et al.* (51)	2015	RCT	160	PORs	Delayed start protocol against the conventional gonadotropin (Gn)-releasing hormone antagonist protocol	Improved clinical pregnancy rate and IVF cycle parameters
Merviel *et al.* (53)	2015	RCT	440	PORs	Contraceptive pill + flare-up GnRH-a protocol compared to the multidose GnRH antagonist protocol.	Pregnancy rates per embryo transferred were not significantly different with the contraceptive pill + flare-up GnRH-a protocol compared to the multidose GnRH antagonist protocol.
Schimberni *et al.* (54)	2016	Trial	250	PORs	Clomiphene citrate plus a high dose of gonadotropins and GnRH antagonist, flexible GnRH antagonist protocol and a short GnRH agonist protocol.	Significantly higher pregnancy rate than the clomiphene and the GnRH antagonist protocol, a higher number of mature oocytes collected, estradiol levels and endometrial thickness.
Toftager *et al.* (57)	2016	Trial	1099	PORs	Risk assessment of severe OHSS in the long GnRH agonist group compared with the short GnRH antagonist protocol.	Patients at risk of OHSS particularly benefit from the short GnRH antagonist treatment
Siristratidis *et al.* (57)	2017	RCT	58	PORs	Mild versus conventional GnRH-agonist and antagonist protocols	Mild ovarian stimulation is inferior to conventional protocols in terms of the numbers of COCs retrieved.

Authors	Year	Study design	Sample size	Study population	Treatment	Outcome
Ashrafi *et al.* (52)	2018	RCT	250	PORs	Delayed start versus standard GnRH-antagonist protocol	Higher fertilization rate and better quality of embryos; lower cycle cancellation but no significant effect on clinical pregnancy rate.
Haas *et al.* (59)	2019	RCT	33	PORs	Double Trigger (GnRH agonist + HCG)	Significant increase in the number of top quality embryos, with a reasonable clinical pregnancy rate, compared to the conventional HCG trigger or the GnRH-ag trigger.
Mak *et al.* (60)	2016	RCT	49	PORs	Recombinant LH (rLH) supplementation vs urinary human chorionic gonadotrophin (uHCG) supplementation when using a fixed GnRH antagonist protocol	No statistically significant difference in cycle cancellation rates, numbers of oocytes retrieved per cycle initiated, fertilization rates, the numbers of embryos obtained per cycle initiated, implantation, clinical pregnancy or live birth rates.
Bastu *et al.* (63)	2016	RCT	95	PORs	Adding letrozole to protocol	Mild stimulation with addition of letrozole was as effective as stimulation with higher doses of gonadotropins alone.
Gizzo *et al.* (65)	2015	RCT	40	PORs	Optimal timing of recombinant luteinizing hormone (rLH) supplementation in GnRH-antagonist treatment	Improved ovarian response, embryo quality and pregnancy rate were achieved by administering rLH independently from the total dose administered.
Humaidan *et al.* (67)	2017	Randomized Clinical Trial	949	PORs	Fixed-ratio combination of recombinant human FSH plus recombinant human LH (follitropin alfa plus lutropin alfa; r-hFSH/r-hLH) vs r-hFSH monotherapy	r-hFSH/r-hLH was associated with a higher live birth rate, whereas r-hFSH was associated with a higher live birth rate for those with mild POR.
Llácer J *et al.* (68)	2020	RCT	60	PORs	Luteal phase ovarian stimulation (LPOS) versus follicular phase ovarian stimulation (FPOS)	LPOS was as effective as FPOS
Caprio *et al.* (71)	2015	Prospective controlled observational trial,	72	PORs	Myoinositol therapy	MI improves ovarian response to gonadotropins
Chen *et al.* (76)	2017	Controlled clinical trial	204	PORs	Minimal stimulation with progestin	Better ovulation control of the dominant follicle but no effect on the quality of oocytes
Bosdou *et al.* (34)	2016	RCT	48	PORs	Pre-treatment with transdermal testosterone	Ovarian response: no more than 1.5 oocytes

RCT=Randomized Clinical Trial; PORs=Poor Ovarian Responders; POR=Poor Ovarian Response; AMH=Anti-Mullerian Hormone; GnRH=Gonadotropin-Releasing Hormone; FSH=Follicle-Stimulating Hormone; OHSS=Ovarian Hyperstimulation Syndrome; COCs=Cumulus Oocyte Complexes; DHEA=Dehydroepiandrosterone; IVF=In Vitro Fertilization; hMG=Human Menopausal Gonadotropin; LZ=Letrozole; GH=Growth Horomone; HCG=Human Chorionic Gonadotropin: LH=Luteinizing Hormone; rLH=Recombinant LH; uHCG=Urinary HCG; r-Hfsh=Recombinant Human FSH; r-Hlh=Recombinant Human LH; LPOS=Luteal Phase Ovarian Stimulation; FPOS=Follicular Phase Ovarian Stimulation; MI=Myoinositol.

POR Management Protocols/Adjuvant Therapies

Anti-Müllerian Hormone

Serum AMH is regarded as a highly sensitive biomarker for ovarian response, with the interpretation of its levels being a useful clinical tool to guide infertility counselling. Magnusson et al. in 2017 performed a randomized controlled trial (RCT) to specify the effect of anti-Müllerian hormone in ovarian response (17). Patients regulated with GnRH agonists and stimulated with recombinant FSH demonstrated neither better ovarian response rate than without administering AMH, nor any decrease in ovarian hyperstimulation syndrome (OHSS), or even the number of cycle cancellations. However, there are no international standards for defining the cut-off values of AMH accordingly to well-established reference intervals, so extrapolation of clinical data to POR population should be made with caution. (17). In this regard, instead of assessing AMH levels alone before ovarian controlled stimulation, it is important to assess both AMH and AFC to predict POR (18).

Clomiphene Citrate

Chemically, clomiphene is a nonsteroidal triphenylethylene derivative that exhibits both estrogen agonist and antagonist properties (19). Song et al. in 2016 conducted a meta-analysis to establish the efficiency of clomiphene citrate in a mildly controlled hyperstimulation protocol (20). The selected four RCTs showed that both live birth and clinical pregnancy occurrence rates were similar, either with clomiphene or without (20).

On the other hand, Kamath et al. in 2017 examined the effectiveness of oral induction medication, such as clomiphene citrate versus gonadotropin-only regimens (21). According to their systematic review, although the use of clomiphene led to a reduction in the amount of gonadotropins required, no conclusive evidence suggested that it could be associated with a significant increase in the incidence of cycle cancellations (21).

Coenzyme Q_{10}

Investigating the effect of anti-oxidant pre-treatment with coenzyme Q_{10}, Xu et al. in 2018 performed an RCT in order to address its beneficial effects in ovarian response and embryo quality (22). Moreover, the combination of dehydroepiandrosterone (DHEA) and coenzyme Q_{10} compared with DHEA alone, during vitro fertilization cycles, improved ovarian response, but no associated improved clinical outcome was demonstrated (23).

Corifollitropin Alpha

A single injection of CFα, a synthetic recombinant glycoprotein, can replace daily FSH injections for the first seven days of controlled ovarian stimulation (COS) as required for IVF (24). Kolibianakis et al. in 2015 carried out a RCT comparing the substitution of follitropin beta by corifollitropin alpha, thus demonstrating that the number of cumulus oocyte complexes (COCs) retrieved was similar in all the groups examined (25). It was then suggested that Corifollitropin alfa simplifies IVF treatment when administered in a GnRH antagonist protocol, since it replaces seven daily FSH injections with a single dose of long acting FSH (25). Comparing the effectiveness of corifollitropin alfa versus daily gonadotropins in PORs undergoing controlled ovarian stimulation according to AFC, Adrisani et al. in 2019 suggested that corifollitropin alfa may be as effective as gonadotropins when AFC >5, while it might be less effective than gonadotropins when AFC ≤5 (26).

Androgens: Dehydroepiandrosterone (DHEA)-Testosterone

Dehydroepiandrosterone (DHEA), is an important precursor of androgen, and has been extensively studied for improving the outcome measures of ovarian stimulation in POR (27). Numerous studies have been published on DHEA supplementation in POR patients. Li et al. in 2015 conducted a meta-analysis evaluating the effects of DHEA on women with diminished ovarian reserve (DOR) who underwent in vitro fertilization with intra

cytoplasmic sperm injection (ICSI) (28). The use of DHEA increased the clinical pregnancy rate, while the impact of DHEA on oocyte retrieval, implantation, and abortion were not significant (28). Nagels et al. in 2015 in their Cochrane review concluded that pre-treatment with DHEA, or its derivative testosterone, may be associated with improved live birth rates in assisted reproductive technology (29). Androgen replacement in advanced-age women with diminished ovarian reserves might improve outcomes. Although DHEA doses range from 50 to 90 mg/day, with a treatment duration ranging from 1 to 12 months, the optimal dose and duration of DHEA remains to be defined (30). Elprince et al. in 2020 studied the effect of DHEA supplementation on improving ovulation among poor responders, and showed a statistically significant effect in the treatment group (31). This may be attributed to the increasing expression of androgen receptor and FSH receptor in granulosa cells after DHEA supplementation (32).

Transdermal testosterone prior to ovarian stimulation significantly increases percentages of live birth and reduces the doses of FSH required (33). In a systematic review and meta-analysis conducted by González-Comadran et al. in 2012, 113 women who were pretreated with transdermal testosterone achieved significantly higher live birth rates and clinical pregnancy rates, and required significantly lower doses of exogenous FSH compared with 112 in the control group (33). Specifically, the RCT of Bosdou et al. in 2016 suggested that pretreatment with 10 mg of transdermal testosterone for 21 days does not improve ovarian response by more than 1.5 oocytes, however, higher doses of testosterone may be more effective (34). Overall, interpreting the results of the meta-analysis by Noventa et al. in 2019 demonstrated that adjuvant testosterone treatment is associated with increased live birth rates and clinical pregnancy rates, as well as the total number of oocytes retrieved (35).

Double Lumen Needle Follicular Flushing System

Despite limited evidence supporting the use of follicular flushing (36), it continues to be common practice in many infertility clinics (37). Von Horn et al. in 2017 examined a double-lumen needle follicular flushing system, comparing it with a single-lumen aspiration needle in IVF patients with poor ovarian response (38). Unfortunately, follicular flushing did not produce a higher oocyte number, while it doubled the duration of the procedure (38).

Double Ovarian Stimulation

Double ovarian stimulation in the same ovarian cycle (DuoStim) starting in the luteal phase could provide more opportunities for retrieving oocytes in a short period of time (39). Madani et al. in 2019 attempted to compare the effectiveness of double stimulation during the follicular and luteal phases in poor responding women (40). According to them, the number of oocytes retrieved after the first and second stimulations did not differ significantly, but the oocytes retrieved after the first stimulation were of better quality (40). Conversely, Vaiarelli et al. in 2019, after reviewing the evidence of DuoStim, suggested that it could be adopted as an effective strategy to maximize the number of oocytes retrieved and subsequently the number of competent embryos in a short timeframe, which is crucial for these patients (41). Although no serious concerns have been raised regarding the safety of DuoStim, Labarta et al. in 2020 underlined the need for further randomized studies to analyze whether similar results could be obtained from two consecutive cycles of ovarian stimulation (42).

Follicle-Stimulating Hormone (FSH)

Lefebvre et al. in 2015 carried out a prospective randomized controlled study to identify the optimal FSH dose for controlled ovarian stimulation in poor responders (43). No major differences were found between the two groups tested (supplementation of 450 IU versus 600 IU gonadotropin per day), regarding the number of oocytes retrieved, pregnancies, implantation or fertilization rate (43). Van Tilborg et al. in 2016 summarized the existing evidence on FSH dosage for PORs treated by a GnRH agonist protocol (44). An individualized

gonadotropin dose ranging from 100-600IU/day depending on basal FSH or AFC does not improve the rates of cycle cancellation, pregnancy, or live births (44). An attempt was made to define an individualized standard FSH dose based on the measurement of various biomarkers, including basal FSH (bFSH), AFC, and AMH (45). However, this study was inconclusive about whether the standard dose of 150 IU could be effective, or a higher dose is needed for ovarian stimulation (45).

Growth Hormone (GH)

GH is described as an adjuvant therapy in in vitro fertilization for poor ovarian responders, but evidence on IVF outcomes has been conflicting. Lattes et al. in 2015 studied the effects of a small dose of GH administered during an IVF cycle in poor responding patients (46). They conducted a prospective self-controlled study in which 64 PORs were administered a small dose of GH, using the same protocol and gonadotropin dose (46). Finally, high pregnancy rates were achieved with no side-effects and at low cost (46). Addition of GH to a conventional IVF protocol with a GnRH antagonist, should be approached with caution (47). In this RCT, one group of patients was given GH in addition to the antagonist protocol, which not only lowered the treatment duration of hMG and GnRH, but also increased the number of oocytes collected and fertilized (47). On the other hand, the small difference in the rate of clinical pregnancy and the low statistical power of the study implied that GH should be supplemented with caution (47). Dakhly et al. in 2016 adopted a different approach (48). The aim of their randomized prospective trial was to define the most suitable protocol including GH for treating PORs (48). The patients involved were allocated into four groups. The group that demonstrated the best outcomes regarding the number of oocytes retrieved and fertilised was the one that received the long agonist protocol with GH (48). Li et al. in 2017 attempted to examine the effectiveness of a GH protocol in relation to the outcome of treating poor responding women (49). Supplementation of GH to the IVF protocol did not provide any significant improvement in the clinical pregnancy and live birth rates, not to mention that the timing of GH administration, as well as the collocation of medications, may have also affected the outcome (49).

Gonadotropin Releasing Hormone (GnRH)

GnRH antagonist administration in the early follicular phase can decrease gonadotrophin levels, which may improve synchronization of follicles, improving ovulation stimulation (50). Maged et al. in 2015 compared a delayed start protocol with a standard protocol that used a gonadotropin releasing hormone antagonist (GnRH antagonist) in poor responding patients (51). The two groups of patients in this RCT either started receiving the GnRH on the first day, or it was delayed until day 8. The results showed an improvement in the IVF cycle parameters and the rate of clinical pregnancy in the delayed group as opposed to the group that began the GnRH dose immediately (51). In this direction, Ashrafi et al. in 2018 attempted to present the differences between a delayed start GnRH protocol and a standard one (52). The trial showed a statistically significant difference in fertilisation rates, in favour of the delayed start protocol. Given the small study sample, further evaluation of their evidence should be performed (52). Merviel et al. in 2015 adopted a more direct approach: among PORs for whom a standard long agonist GnRH protocol had failed, they applied and compared the results of two different protocols: a contraceptive pill with a flare-up agonist GnRH, and a GnRH antagonist (53). Even though the embryo transfers were greater with the first protocol than the second, their pregnancy and implantation rates were similar in relation to the woman's age and lifestyle. Since the prognostic factors for this protocol were maternal age <36, no tobacco consumption, a total FSH/hMG dose <5,000 IU, and endometrial thickness >10 mm, customizing the policy of ovarian stimulation according to the woman's age and lifestyle could certainly improve outcomes (53). Likewise, Schimberni et al. in 2016 examined three different protocols on poor responders: a short

GnRH agonist, a GnRH antagonist with high doses of gonadotropins and clomiphene citrate, and a flexible GnRH antagonist, respectively (54). Of the three groups, the one that had the short GnRH agonist had the highest rate of pregnancy and lowest cost of therapy, in contrast to clomiphene citrate which should be avoided due to its very low success rate and high costs (54). The challenge of selecting the gonadotropin starting dose was met with success by Li et al. in 2021 (9). Although several nomograms have been developed to estimate the appropriate gonadotropin starting dose in GnRH agonist protocols adopted in IVF, no nomogram was suitable for GnRH antagonist protocols (9). Another comparison between two different protocols was performed by Siristratidis et al. in 2017 (55). In their study, they evaluated the effect of a mild GnRH agonist/antagonist protocol in comparison to a conventional protocol. The outcome, however, was that the number of COCs was lower than with conventional stimulation, thereby showing its inferiority to the conventional protocol (55). Similarly, Lambalk et al. in 2017 investigated which would be the better protocol of a long agonist GnRH and a GnRH antagonist (56). To answer this question, they carried out a systematic review and meta-analysis. For poor responders, it was revealed that the antagonist protocol was associated with a smaller incidence of OHSS and similar rates of pregnancy (56). Notably, OHSS is a possible side-effect of a GnRH protocol. For that reason, Toftager et al. in 2016 performed a study to assess the risk of OHSS when using the short antagonist and the long agonist GnRH protocols (57). Women less than forty years old and infertile were randomly allocated to GnRH antagonist or agonist protocols. OHSS, rated as severe, moderate or mild, appeared less often in the antagonist group than the agonist, so patients at risk of OHSS particularly benefited from the short GnRH antagonist treatment (57).

Human Chorionic Gonadotrophin (hCG)

Kasum et al. in 2016 examined the combination of a GnRH agonist along with a human chorionic gonadotrophin (hCG) trigger in order to achieve oocyte maturation and retrieval (58). This dual trigger could be a possible treatment for empty follicle syndrome and PORs, since it is associated with increased live births and a better quality of preserved embryos (58). Double triggering was also studied by Haas et al. in 2019 (59). Thirty-three PORs were allocated to three random groups with different protocols regarding the addition of GnRH agonist in combination with hCG. The group that was administered the double trigger protocol showed a higher number of top-quality embryos than the other two. However, the small sample size of the study requires further evidence to validate its clinical implementation (59). Mak et al. in 2017 conducted a double-blinded study to examine the effects of urinary human chorionic gonadotrophin (uhCG) compared with the supplementation of mid-follicular phase recombinant luteinizing hormone (rLH) (60). Unfortunately, clinical birth rates and other parameters of the IVF cycle were similar, except for the live birth rate per cycle, which was higher for the uhCG group. Further RCTs are required to verify these results (60).

Letrozole

Letrozole is a highly selective, non-steroidal aromatase inhibitor. It prevents estrogen syntheses by inhibiting the aromatase enzyme activity, thus increasing the expression of FSH receptors on the follicle (61). Letrozole administration could improve pregnancy rates in conventional GnRH antagonist protocols, as demonstrated in a recent meta-analysis by Qin et al. in 2021 (62). Bastu et al. in 2016 carried out a RCT to examine the impact of adding or not adding letrozole to a standard ovulation stimulation protocol, which included POR patients who received three different gonadotropin doses during ovulation stimulation (63). Mild stimulation with the addition of letrozole was as effective as stimulation with higher doses of gonadotropins alone in this patient population (63). Conversely, Kamath et al. in 2017 did not provide sufficient evidence regarding the beneficial supplementation of

conventional GnRH agonist or antagonist protocols concerning live-birth or pregnancy rates (21).

Recombinant Luteinizing Hormone (rLH)

While the need for FSH in ovarian stimulation is evident, a question remains regarding the role of rLH in different IVF population groups (64). Gizzo et al. in 2015 attempted to determine the optimal timing to administer rLH during an in vitro fertilization cycle (65). Although increased endometrial thickness appeared when rLH was administered at the beginning of the follicular phase, the highest ovarian response occured when rLH was administered in the mid-to-late phase. The study's limited size and lack of information regarding the differences in intra-follicular growth factors suggest that further large-scale clinical trials should be conducted (65). Moreover, the definition of the LH threshold in GnRH analogue treated cycles, as well as identification of which subgroups of women could benefit from adjuvant rLH treatment, have not been clearly answered (66). Humaidan et al. in 2017 evaluated the effectiveness of COS comparing a fixed-ratio combination of recombinant human FSH plus recombinant human LH (r-hFSH/r-hLH) with that of r-hFSH monotherapy (67). The incidence of pregnancy outcome failure was significantly lower in the r-hFSH/r-hLH group than in the r-hFSH group, but live birth rates were similar in both groups (67).

Luteal Phase Ovarian Stimulation (LPOS)

Llácer et al. in 2020, attempting to assess the efficacy of LPOS compared with follicular phase ovarian stimulation (FPOS), achieved comparable results (68), but they are probably not conclusive, similar to those of Chen et al. in 2021 (69), since the number of oocytes collected was similar with both luteal and follicular stimulation (68).

Myo-Inositol (MI)

Inositols are a family of carbocyclic polyalcohols, with nine possible stereoisomers, including MI (70). MI has proven useful in issues related to female infertility and in sustaining physiological pregnancy (70). Caprio et al. in 2015 performed a prospective controlled observational trial to examine the effectiveness of myoinositol on ovarian function in PORs (71). The patients were divided into two groups. In the treatment group, 38 patients were enrolled who had been taking MI (4 g) + folic acid (FA) (400 μg) for the previous 3 months, while the control group included 38 patients taking FA (400 μg) alone for the same study period (71). MI supplementation in poor responders resulted in an increased number of oocytes retrieved (71), as well as in implantation and pregnancy rates (72). Similar positive results regarding ovarian response were shown after the double-blinded randomized controlled study by Mohammadi et al. in 2021 (73) who allocated the two study groups according to Caprio et al. in 2015 (71).

Progesterone

In an attempt to develop new stimulation regimens, the administration of endogenous and exogenous progesterones was used in order to block the LH surge during ovarian stimulation (74). Massin et al. in 2017 found that this technique does not affect the number of oocytes collected or the quality of the embryos obtained (74). However, the main disadvantage observed was that it requires total freezing and delayed transfer (74). Advancing our knowledge in this direction, progesterone administration was found to inhibit granular cell proliferation and antral follicle growth during ovarian stimulation via phosphatidylinositol-3 kinase (PI3K)/protein kinase B (AKT) and mitogen-activated protein kinase (MAPK) pathways (75).

Progestin (P)

Since the efficacy of progestin on poor responders had not yet been extensively examined, Chen et al. in 2017 performed a clinical trial in order to ascertain the outcomes of progestin-primed minimal stimulation on PORs (76). The study provided evidence showing that stimulation through progestin

is able to control the ovulation of the dominant follicle, while not affecting oocyte quality (76). So, progestine could be used as a possible means to prevent premature ovulation (76). Specifically, progestin-primed ovarian stimulation using 4 versus 10 mg of medroxyprogesterone acetate per day is comparable, and did not differ in terms of the number of oocytes retrieved and pregnancy outcomes (77). Therefore, progestin-primed ovarian stimulation could be the first choice for ovarian stimulation due to its better control of LH concentrations, lower costs, and easier oral and not intravenous administration (78). Finally, the most representative strategies and pharmaceutical stimulation protocols proposed in the current literature for POR are summarized in Table 2. It should also be mentioned that controlled ovarian stimulation for fertility preservation in patients with malignancy could be also challenging. Although the type of cancer has not been proven to significantly affect ovarian reserve and ovarian response (79), patients with high-grade cancer have a decreased number of retrieved mature oocytes and cryopreserved embryos (80).

Conclusion

POR management represents a great challenge for assisted reproduction technology specialists. Due to the lack of a standard definition, as well as the heterogeneity of the factors associated with POR cases, no consensus has been reached on the most beneficial therapeutic intervention to overcome poor oocyte retrieval. Although many strategies and pharmaceutical treatments have been suggested to manage POR, none has been proven superior to the others, in terms of the number of oocytes retrieved per ovarian cycle, the number of competent embryos, or live birth rates. Further large-scale randomized studies are needed to validate the experimental techniques in the search for successful individualized treatment regimens.

What Is Already Known on This Topic:

Patients defined as " poor responders" show minimal response to controlled ovarian hyperstimulation, although there is no distinct/standard definition of poor ovarian response (POR). Although infertility specialists are endeavoring to improve cycle outcomes in poor responders by adopting multiple management strategies, the estimated risk of cycle cancellation is still about 20%.

What This Study Adds:

This review summarizes all the latest studies published between 2015 and 2021 concerning the management protocols adopted for POR cases. None has been proven superior to the others, in terms of the number of oocytes retrieved per ovarian cycle, the number of competent embryos or live birth rates. Further large-scale randomized studies are needed to validate experimental techniques in the search for successful individualized treatment regimens.

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